REMARKS

Claims 1 and 3-5 are pending in the present application.

I. The Claims Are Clear And Definite

Claims 1 and 3-5 are rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention. The Office asserts that "it is not clear how the sample is processed or assayed as there are no actual processing and assaying steps claimed" (see, Final Rejection at page 2). Applicant traverses the rejection and respectfully requests reconsideration because the claims are clear and definite.

Persons of ordinary skill would have no difficulty in determining whether a particular method of diagnosing pre-eclampsia meets the criteria recited in claim 1. Accordingly, the claims are definite within the meaning of §112. *In re Mercier*, 185 USPQ 774 (C.C.P.A. 1975) (claims sufficiently define an invention so long as one skilled in the art can determine what subject matter is or is not within the scope of the claims).

Applicant respectfully points out that the description of the invention is the role of the specification, not the claims. *Orthokinetics, Inc. v. Safety Travel Chairs, Inc.*, 1 USPQ.2d 1081 (Fed. Cir. 1986). In addition, the amount of detail required to be included in the claims is not to be viewed in the abstract but in conjunction with the specification. *Shatterproof Glass Corp. v. Libbey-Owens Ford Co.*, 225 USPQ 634 (Fed. Cir. 1985). As such, the specification contains examples of "processing" a sample of maternal saliva collected from a subject prior to assaying. For example, the paragraph 0016 bridging pages 3 and 4 of the specification teaches that the collected sample of saliva is transported and processed by a laboratory where the tube may be centrifuged so that it is ready for assay. Thus, centrifugation is one example of "processing." Further, paragraph 0037 of the specification teaches that upon collection of saliva, a swab containing the saliva is returned to the insert in the Salivette®, which is appropriately labeled. The swab is then kept cool in a refrigerator, for example, until it is transported and processed by the laboratory. Paragraph 0038 further teaches that upon receipt at the laboratory and after laboratory and patient information is collected from the tube label, the Salivette® tube with the

swab insert is centrifuged which results in a clear sample of mixed saliva that is ready for assay. Thus, the specification amply teaches one skilled in the art "processing" of the collected sample. Indeed, samples of almost any type of tissue usually undergo some type of appropriate processing well known to those of skill in the art prior to actually assaying the sample for a particular analyte.

In addition, the specification is replete with examples of assaying the sample for the concentration of urate present. For example, paragraph 0017 teaches that levels of urate in the biological sample can be measured by any suitable test or biological assay, including a dip stick test, the timed end point method, or the dry test method, each of which are further explained in paragraphs 0018-0021. Thus, there can be no question that Applicant provides ample description in the specification of assaying the sample for the concentration of urate present.

Thus, claims 1 and 3-5 are clear and definite. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

II. The Claimed Invention Is Not Obvious

Claims 1 and 3-5 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the combination of each of the following references: 1) WO 00/08207 (hereinafter, the "Lee reference"); 2) U.S. Patent No. 6,753,159 (hereinafter, the "Lee patent"); 3) Fossati et al., Clin. Chem., 1980, 26, 227-231 (hereinafter, the "Fossati reference"); 4) Owen-Smith et al., The Lancet, 1998, 1, 1 (hereinafter, the "Owen-Smith I reference"); and 5) Owen-Smith et al., Salivary Urate as an Indicator of Metabolic Stress, (hereinafter, the "Owen-Smith X reference"); in further view of each of Dunlop et al., Brit. Med. J., 1978 (hereinafter, the "Dunlop reference"), Schuster et al., Gynecol. Obstet., 1981, 12, abstract (hereinafter, the "Schuster reference"), and Pipkin et al., J. Hypertension, 2004, 22, 237-239 (hereinafter, the "Pipkin reference"). The Office mistakenly asserts that it would have been *prima facie* obvious for one skilled in the art to have "measured urate levels in maternal saliva in a method for diagnosing preeclampsia because the art teaches that there is a clear association between urate concentration levels and preeclampsia" and that the "art teaches that urate is widely distributed in extracellular fluid such as saliva" (see,

Final Rejection at page 4). Applicant traverses the rejection and respectfully requests reconsideration.

As a preliminary matter, Applicant notes that claims 1 and 3-5 were alleged to be obvious in the Office Action dated December 15, 2008 over the combination of the same references as cited herein except for the addition of the Owen-Smith X reference in the present obviousness rejection. Applicant reminds the Office that the Owen-Smith X reference IS NOT prior art that can be relied upon by the Office. Below is a paragraph reproduced from Applicant's response filed April 15, 2009 that discusses the Owen-Smith X reference:

> As further evidence of this prejudice in the art against measuring saliva for diagnosing pre-eclampsia, Applicant has a hand-written letter from Dr. Jonathan Hooker, a consultant obstetrician at St Richard's Hospital (the Royal West Sussex Trust, Chichester, United Kingdom), dated 12 December 1997. A copy of this letter and a transcript thereof is enclosed herewith. The inventor, Dr. Owen-Smith, a consultant rheumatologist also at St Richard's Hospital, had requested Dr. Hooker's opinion on an observation of increased salivary urate levels in a patient with pre-eclampsia. **Dr. Owen-Smith sent Dr. Hooker a draft of the paper that was later published in the Lancet (i.e., the Owen-Smith reference). A copy of the unpublished draft paper is enclosed and states that salivary urate was found to be reduced on day 3 post-delivery.** Dr. Hooker's response to the suggestion that salivary urate levels were an indicator of pre-eclampsia was "Increased urate in pre-eclampsia is more to do with renal function (see enclosed from Michael de Swiet's "Medical Disorders on Obstetric Practice") rather than purine metabolism" (see, typed version of hand written note, dated 12 December 1997 from Dr. Jonathan Hooker to Dr. Brian Owen-Smith and enclosed extract from de Swiet). In addition, Dr. Hooker suggested that "the changes in [salivary] urate levels will not be significant" (see, typed version of hand written note, dated 12 December 1997 from Dr. Jonathan Hooker to Dr. Brian Owen-Smith). As a result of Dr. Hooker's comments, **the pre-eclampsia observation was not published** and work in this area was temporarily ceased by the inventor. Therefore, it is clear that even with a case of pre-eclampsia included in a draft paper, a senior obstetrician skilled in the art did not think that salivary urate was a sensitive indicator of purine metabolism and, hence, would be useful in diagnosing pre-eclampsia.

(Emphasis added). The draft paper authored by Dr. Owen-Smith and sent to Dr. Hooker for critique is the "Owen-Smith X reference" now relied upon by the Office in the most recent

Office Action, which was **never published** in its present form. Indeed, the comment in the Owen-Smith X reference regarding salivary urate as an "indicator of pre-eclampsia", which is specifically relied upon by the Office at page 3, lines 17 to 18 of the Office Action, was taken out before publishing other observations in the Lancet reference (i.e., the Owen-Smith I reference). The publication date of 1981 attributed to the Owen-Smith X reference by the Office in the Office Action is clearly incorrect since this document was never published and hence has no publication date. Accordingly, there is no basis in the Final Rejection for the assertion that salivary urate can be used for diagnosing pre-eclampsia, as incorrectly stated in the Office Action on page 4, lines 3 to 4.

To provide additional reasoning for the non-obviousness of the claimed invention, Applicant hereby repeats the response to the previous Office Action below for the Office's convenience.

Whilst an understanding of the mechanism of action is not required for patentability in the United States, it may be useful in establishing non-obviousness in view of the cited references, particularly since the Office is making assumptions and reaching conclusions that the skilled person in the art would not.

A first point is in regard to the field in question when referring to pre-eclampsia. The Office appears to believe that the field in question is obstetrics. Applicant reminds the Office that when referring to urate metabolism, rheumatology and biochemistry are as well quite applicable. Applicant's application combines these two disparate fields in a non-obvious way to reach the claimed invention.

The urate, which refers to the salt form of "uric acid", in the body is referred to as the urate, or uric acid, pool. The level of urate in this pool is a balance between production and elimination (see, for example, the Owen-Smith reference, and Seitchik, Am. J. Obst. Gynecol., 1956, 72, 40-47, a copy of which is provided herewith). Urate is synthesized from amino acid and glucose metabolism, largely derived from the diet. Urate is also produced as a result of the breakdown of nucleoproteins that occurs with the normal turnover of cells in the body -- referred to as purine metabolism (see Seitchik reference). In humans, urate is the final oxidation product

of purine metabolism. The excess urate produced therefore needs to be excreted by the kidneys (see, Xiangwei et al. J. Mol. Evolution, 1992, 34, 78-84, a copy of which is provided herewith).

When considering changes in the urate pool, obstetricians consider these changes to be brought about by changes in renal function during pregnancy (see, de Swiet, extract from Medical Disorders of Pregnancy, 1989, a copy of which is provided herewith). This, however, represents a fundamental misunderstanding of urate metabolism and fails to take into account other factors that can affect the urate pool. More specifically, of the urate eliminated from the body each day, two thirds are eliminated in the urine and one third is eliminated in the gut via saliva and intestinal secretions where it undergoes bacterial uricolysis (see, for example, the Owen-Smith reference). In addition, during sleep, more urate is excreted in the gut than in the kidneys as renal excretion (urine excretion) decreases (see, Owen-Smith et al., Ann. Rheum. Dis., 1981, 40, 523-24, hereinafter, the "Owen-Smith II reference," a copy of which is provided herewith). The obstetric art, however, fails to take this elimination in the gut into account (see, for example, the de Swiet reference).

The Lee reference, the Lee patent, and the Fossati reference report methods of detecting urate in a biological sample. However, two important pieces of information are missing from each of these documents: 1) none of these references teach using samples of saliva to detect levels of urate; and 2) none of these references teach a link between the levels of urate in the body (be it in blood or saliva or indeed any biological sample) and pre-eclampsia. In order to account for this deficiency, the Office combines the teachings of these references with the Owen-Smith reference to reach the conclusion that samples of saliva can be used to measure the level of urate in the body. One skilled in the art, however, would not combine these references in the manner set forth b the Office. This is partly because the skilled person working in the field of obstetrics is not concerned with the salivary excretions of urate since they consider changes in plasma urate levels to be due to changes in renal function. Indeed, the authors of the Owen-Smith reference are rheumatologists (Brian Owen-Smith and James Read) and biochemists (Jeremy Quiney). The authors discuss the possibility of using salivary urate to measure purine metabolism. An obstetrician, however, would not use this reference to reach the conclusion that salivary urate could be used to diagnose pre-eclampsia because obstetricians do not consider

purine metabolism to be relevant to changes in plasma urate concentrations. Furthermore, the Owen-Smith reference does not suggest a link between levels of urate in the body and pre-eclampsia. Consequently, to account for this additional deficiency, the Office combines the aforementioned references with the Pipkin, Dunlop, and/or Schuster references, which one skilled in the art would not do. The Office appears to be of the opinion that the Pipkin, Dunlop, and Schuster references all describe a correlation between plasma urate levels and pre-eclampsia. This relationship, however, is poorly characterized in the art of obstetrics and there are numerous contradictions in the art.

In making the arguments presented in the Office Action, the Office is working under several incorrect assumptions, each of which is addressed below in detail.

1. Relationship between plasma urate levels and pre-eclampsia

First, the Office incorrectly assumes that there is a clear association between plasma urate and pre-eclampsia. The Office cites the Pipkin, Dunlop, and Schuster references in this regard. The relationship between plasma urate and pre-eclampsia, however, is far from clear and there are several contradictions in the art.

The Pipkin reference suggests that serum uric acid (SUA) is increased in women with clinically evident pre-eclampsia (see, page 238, column 1, second paragraph, lines 1 to 2). The Pipkin reference, however, also makes several statements indicative of the fact that, at the time of publication, the relationship between plasma urate levels and pre-eclampsia was not well understood. For example, the Pipkin reference states that "…there is no consensus as to the sensitivity and specificity of hyperuricaemia as a prognostic indicator for future pre-eclampsia. Indeed, a review article a decade ago concluded specifically that 'as for other signs of pre-eclampsia, hyperuricaemia is non-specific'" (see, page 238, first column, second paragraph, lines 2 to 7).

Furthermore, the Pipkin reference cites a study of nulliparous women (women who have not had a child) and states "A prospective study of 1366 nulliparous women in whom SUA was measured between 15 and 24 weeks gestation and again between 25 and 34 weeks gestation did not identify SUA as a useful predictor of future disease" (see, page 238, first column, second

paragraph, lines 7 to 11). The Pipkin reference goes on to state "one prospective study from first trimester pregnancy [in which] urate production was actually lower in women who went on to develop pre-eclampsia" (see, page 238, column 2, paragraph 3 lines 8 to 10).

Thus, the Pipkin reference clearly demonstrates that the relationship between pre-eclampsia and plasma urate levels was not well understood at the time of publication.

The Dunlop reference further complicates the notion that raised plasma urate levels are associated with pre-eclampsia. Indeed, the Dunlop reference discusses how one group of practitioners would consider a particular rise in plasma urate concentration as indicative of pre-eclampsia, whereas another group of practitioners would consider that same rise to be part of the normal variations that occur during pregnancy (including diurnal variations seen in some patients). No explanation for daily variations is given other than to say plasma urate is subject to normal physiological variability. The skilled person would consider the Dunlop reference as adding to the unsuitability of plasma urate as a diagnostic agent in pre-eclampsia.

The Schuster reference discusses the relationship between plasma urate levels and fetal birth weight. The authors suggest that "These findings suggest, in terms of fetal development, changes in renal retention of urate may be an additional predicting factor for fetal development as important as hypertension alone" (see, lines 12 to 15 of the abstract). The authors do not make a clear correlation between raised plasma urate levels and pre-eclampsia. Rather, the authors investigated the effect of renal retention of urate on birth weight and the effect of hypertension on birth weight.

The contradiction in association between increased plasma urate levels and pre-eclampsia can be seen in other documents in the art. For example, in Connon and Wadesworth, Aust. N. Z. J. Obstet. Gynaec., 1968, 8, 197-201 (a copy of which is provided herewith), in a survey of 261 patients with pre-eclampsia diagnosed by blood pressure of 140/90 or more, generalised oedema and proteinuria without urinary infection concluded: "while an elevated serum urate from 6.0 mg/ml to 10 mg/ml was suggestive of pre-eclampsia, and an increasing level was highly significant, **half the patient with pre-eclampsia had normal serum urate levels**" (emphasis added, see page 200).

In addition, the Seitchik reference reports that in many women with toxemia (of which pre-eclampsia is a symptom), the plasma urate level remains fairly constant due to a number of antagonistic factors that affect plasma urate levels:

> **It is obvious from the foregoing that the determination of plasma urate concentration can hardly be of much clinical usefulness.** The factors operative in the production of a particular level of plasma urate concentration in an individual patient are multiple. The rate of destruction of urate, the rate of excretion of urate, the state of nitrogen metabolism, and the available volume of distribution of urate – all these factors are operative in every patient with toxemia, and the metabolic design is such that the plasma urate concentration tends to remain within normal limits.

(see page 46, paragraph 4, emphasis added).

Therefore, it is clearly incorrect for the Office to consider there to be a clear correlation between plasma urate concentrations and diagnosis of pre-eclampsia. Indeed, there are many contradictions in the art that would provide one skilled in the art with serious doubt as to the suitability of plasma urate in diagnosing pre-eclampsia.

2. Obstetrics versus rheumatology, and prejudice in the art of obstetrics

Second, the Office has not taken into consideration the prejudice in the art of obstetrics against using saliva as a source of urate to determine urate levels in the body and, hence, potentially diagnosing pre-eclampsia. This prejudice is due to a fundamental misunderstanding on the part of obstetricians regarding the nature of urate metabolism and the mechanisms involved in controlling urate levels in the body.

The relevant "art" when discussing pre-eclampsia is obstetrics (the surgical specialty dealing with the care of a woman and her child during pregnancy, child birth, and the period shortly after birth). In contrast, the relevant "arts" when discussing urate metabolism are rheumatology and sports and exercise medicine. Rheumatology has long since studied blood urate levels but has never associated hyperuricaemia with pre-eclampsia (see, Dieppe et al.,

sections "Associations of Hyperuricaemia" and "Common Causes of Hyperuricaemia" in Rheumatology Medicine, 1985, a copy of which is provided herewith).

Rheumatologists understand that, in times of oxidative stress (for example during exercise), purine metabolism increases and hence the level of urate in the body increases (see, for example, the Owen-Smith reference, which teaches that at times of oxidative stress such as exercise, levels of urate in the saliva can be used to measure purine metabolism). The present application works, at least partly, on the hypothesis that a pre-eclamptic mother is placed under oxidative stress and hence purine metabolism (and consequently urate production) increases. Therefore, the present application proposes for the first time to use salivary urate to measure purine metabolism in pregnant women as a diagnostic indicator for pre-eclampsia.

In contrast, the art of obstetrics teaches that diagnosis of pre-eclampsia is based on hypertension, in association with protein in the urine and oedema. For example, the Royal College of Obstetricians and Gynaecologists in "The management of severe pre-eclampsia/eclampsia", published in March 2006, states "Pre-eclampsia is pregnancy-induced hypertension in association with proteinuria (>0.3 g in 24 hours) ± oedema and virtually any organ system may be affected" (see page 1, third paragraph).

Furthermore, obstetricians consider the main factor controlling plasma urate levels in pre-eclamptic women as being the result of changes in renal excretion. The de Swiet reference reports:

> Normal pregnancy induces relative hypouricaemia. Plasma urate concentrations decrease by over 25 per cent as early as week 8 of pregnancy, but increase again during the third trimester to attain levels close to the non-pregnant mean. **The main reason for this is alteration in the renal handling of urate** which, although freely filtered, is subsequently so actively re-absorbed that only about 10 per cent of the original filtered load appears in the urine. Later in pregnancy the kidney appears to excrete an even smaller proportion of filtered urate load and **it is this increase in net reabsorption that is associated with an increase in plasma urate concentration**.

(see, page 231, column 1, paragraph 2, emphasis added).

Nowhere in the obstetric art is it taught that one third of urate is eliminated in the gut via saliva and intestinal secretions. The above extract also demonstrates that there is a poor

understanding of the mechanisms surrounding purine metabolism and the effect of oxidative stress on the levels of urate in the body. Although the Owen-Smith reference suggests that salivary urate can be used to measure purine metabolism, an obstetrician believes the changes in plasma urate are due to changes in renal excretion and not due to changes in purine metabolism. Consequently, if an obstetrician wanted to measure the levels of urate in the body, he or she would not look to the saliva as a bodily fluid in which to measure levels of urate. .

Furthermore, in Hill, Mayo Clin. Proc., 1978, 53, 743-751 (a copy of which is provided herewith), it is stated "thus, an alteration in excretion of uric acid is most likely involved in the pathogenesis of pre-eclamptic hyperuricaemia. Because pronounced changes in uricolysis would not be expected in pre-eclampsia, investigators have focused on renal function during pregnancy-induced hypertension" (see, page 748, paragraph 3). Therefore, it is clear that obstetricians do not believe changes in urine metabolism to be significant in pre-eclampsia. Hence, they would not use the teachings of the Owen-Smith reference (which suggests that salivary urate can be used to measure purine metabolism) to use saliva as a source of biological fluid for measuring changes in bodily urate in a pregnant women.

As further evidence of this prejudice in the art against measuring saliva for diagnosing pre-eclampsia, Applicant has a hand-written letter from Dr. Jonathan Hooker, a consultant obstetrician at St Richard's Hospital (the Royal West Sussex Trust, Chichester, United Kingdom), dated 12 December 1997. A copy of this letter and a transcript thereof is enclosed herewith. The inventor, Dr. Owen-Smith, a consultant rheumatologist also at St Richard's Hospital, had requested Dr. Hooker's opinion on an observation of increased salivary urate levels in a patient with pre-eclampsia. Dr. Owen-Smith sent Dr. Hooker a draft of the paper that was later published in the Lancet (i.e., the Owen-Smith reference). A copy of the unpublished draft paper is enclosed and states that salivary urate was found to be reduced on day 3 post-delivery. Dr. Hooker's response to the suggestion that salivary urate levels were an indicator of pre-eclampsia was "Increased urate in pre-eclampsia is more to do with renal function (see enclosed from Michael de Swiet's Medical Disorders on Obstetric Practice") rather than purine metabolism" (see, typed version of hand written note, dated 12 December 1997 from Dr. Jonathan Hooker to Dr. Brian Owen-Smith and enclosed extract from de Swiet). In addition, Dr.

Hooker suggested that "the changes in [salivary] urate levels will not be significant" (see, typed version of hand written note, dated 12 December 1997 from Dr. Jonathan Hooker to Dr. Brian Owen-Smith). As a result of Dr. Hooker's comments, the pre-eclampsia observation was not published and work in this area was temporarily ceased by the inventor. Therefore, it is clear that even with a case of pre-eclampsia included in a draft paper, a senior obstetrician skilled in the art did not think that salivary urate was a sensitive indicator of purine metabolism and, hence, would be useful in diagnosing pre-eclampsia.

As a consequence of this prejudice, it can be seen that it would not be obvious to a person of skill in the art (an obstetrician) to look to salivary urate levels to diagnose pre-eclampsia in pregnant women. This is because the obstetrician believes changes in body urate are due to changes in renal excretion and not changes in purine metabolism. Further evidence that the art of obstetrics only takes into account changes in renal function when assessing changes in urate levels in the body can be seen in de Jong et al., J. Perinat. Med., 1997, 25, 347-352 (a copy of which is provided herewith). The de Jong reference is cited by the Pipkin reference as evidence that uric acid production is lower in women that went on to develop pre-eclampsia (see, page 238, column 2, paragraph 3 lines 8 to 10). In the de Jong reference, the authors make the assumption that the amount of urate produced each day is the amount collected in the urine: "Uric acid was measured in serum and 24-hours urine samples (uric acid excretion)…Uric acid excretion was significantly lower in the first trimester…The data show diminished uric acid production in patients who will likely develop pre-eclampsia" (see abstract). From this reference, it is clear that the obstetric art fails to take into account extrarenal elimination of urate (for example in the gut) and, therefore, would not consider salivary excretions of urate to be an accurate or reliable measure of urate in the body.

Given this prejudice in the art of obstetrics, it would not be obvious for one skilled in the art to combine the teachings of the Owen-Smith reference, which reports that salivary urate can be used to measure purine metabolism, with any of the cited references. Thus, one skilled in the art would not combine the cited prior art documents as the Office has done to arrive at the claimed invention.

Even if one skilled in the art were to do this (which he or she would not), he or she

would not expect a test comprising the detection of urate levels in saliva to diagnose pre-eclampsia to work (in contrast to the Office's opinion), since obstetricians believe changes in bodily urate are due to changes in renal excretion and excretion in the saliva is irrelevant (see, evidence from Dr. Hooker, above).

Furthermore, the claims, as amended herein, recite that the level of urate detected in the sample be compared with a normal control value. Therefore, even in one skilled in the art were to combine the references in the same manner as the Office (which one skilled in the art would not), the skilled artisan would still not arrive at the claimed invention.

3. Plasma versus saliva

Third, the Office has not taken into consideration the fundamental differences between blood plasma and saliva and the different mechanisms by which urate levels can be affected in each of these bodily fluids. The Office has also not taken into account the differences in types of "biological sample" and has assumed that characteristics of one type of "biological sample" can be used to determine the nature and composition of a different type of "biological sample". Indeed, the factors and mechanisms controlling the composition of different biological samples are distinct.

The extracellular fluid compartment comprises blood plasma and interstitial fluid (see, Ganong, extract from Review of Medical Physiology, 1963, Lange Medical Publications, Los Altos, Californian, illustration on page 4 captioned "Electrolyte composition of body fluids in mEq/liter", a copy of which is provided herewith). Much of the urate found in the blood plasma is protein bound and is retained in the blood vasculature (see Campion et al., Arthritis and Rheumatism, 1975, 18, 747, a copy of which is provided herewith). In contrast, saliva is part of a sub-compartment of the extracellular fluid known as interstitial fluid and is distinct from the plasma.

One skilled in the art (an obstetrician) would consider plasma levels of urate to be determined by changes in renal excretion (see, extract from the de Swiet reference, the Hill reference and the evidence from Dr Hooker). In contrast, the Owen-Smith reference states that "…salivary urate is a sensitive indicator of purine metabolism when compared with blood urate"

(see, last paragraph). Therefore, it is clear that if one skilled in the art (an obstetrician) wanted to measure the levels of plasma urate in the body, he or she would not use a sample of saliva as an alternative to measuring plasma levels of urate directly. This is because the obstetrician believes the levels of plasma urate to be determined by changes in renal excretion and salivary excretions are irrelevant. It is only through inventive skill the inventor, Dr. Owen-Smith, has combined the knowledge of rheumatology and sport and exercise medicine with that of obstetrics to arrive at the claimed invention.

Furthermore, the fetus is submerged in amniotic fluid, which is derived from interstitial fluid (see, Modena & Fieni, Acta Bio. Medica. Ateneo. Parmense, 2004, 75, Suppl. 1, 11-13, a copy of which is provided herewith). Consequently, it is proposed as part of the current application that it is the level of urate in the interstitial fluid that is important in pre-eclampsia, and not the levels of plasma urate.

In addition to the differences between plasma and saliva, there are many other "biological fluids" in which zero or only trace urate is found. For example, faeces is a "biological sample", but only trace levels of uric acid is found in this "biological sample", even in patients with gout in which levels of urate are elevated. Sorensen, J. Clin. Lab. Invest., 1960, 12, Supp. 54, 186-194 states: "After the intravenous injection of uric acid-C14, the isotope found to exist in the saliva and the feces.... Only a trace, if any at all, of uric acid could be detected in the feces" (see, page 192, paragraphs 2 and 3).

Therefore, it is clear that the Office's assumption that the composition of one "biological sample" can be used to determine and predict the composition of another "biological sample" is unfounded and should be reconsidered.

4. Men vs. women and gout vs. pre-eclampsia

Fourth, the Office has incorrectly assumed that information regarding one group of patients and disease (for example males with gout, which is studied by rheumatologists) can be used to help diagnose a completely separate condition in an entirely different population of patients (women with pre-eclampsia, which is studied by obstetricians).

Although rheumatologists have long since studied blood urate levels and the mechanisms that effect hyperuricaemia and understand that purine metabolism is an indicator of oxidative stress, it would be far from obvious to use this information in the field of obstetrics to test for pre-eclampsia. This is because most of the studies involving plasma urate levels have been concerned with gout. Gout occurs mostly in men above the age of 50 and is characterized by painful joints due to uric acid crystal deposition in joints and the surrounding tissues. However, the physiology of middle aged to elderly males is completely distinct from that of pregnant women. One skilled in the art would not readily use information gained from studying men with gout in the diagnosis of pre-eclampsia in pregnant women. Indeed, this is evidenced by Dr. Hooker's reaction to Dr. Owen-Smith's hypothesis that purine metabolism played a role in pre-eclampsia.

It is only through genuine inventive skill that a connection was able to be made between purine metabolism, levels of urate in maternal saliva, and a mother's likelihood of developing pre-eclampsia that lead to the current invention. It challenges prevailing prejudices in the field of obstetrics and puts forward a novel and non-obvious strategy for diagnosing pre-eclampsia in pregnant women.

5. Day/night variation in salivary levels of urate

Fifth, the claims, as amended herein, now refer to the comparison of the level of urate detected with a "normal control value". This takes into account natural diurnal and day/night variations that occur in body urate levels. Even if one skilled in the art were to conclude that raised urate levels in the body could be used to detect pre-eclampsia (which is certainly not conceded) and that one skilled in the art would combine the disparate teachings of rheumatology and obstetrics to test for pre-eclampsia by determining the level of urate in a saliva sample (which we continue to assert that he or she would not), he or she would still not arrive at the claimed invention for the following reasons.

The claims, as amended herein, now recite that the level of urate measured in a sample of maternal saliva is compared with a "normal control value." It is explained in the application that changes in urate production and excretion drastically affect the level of urate found in the

plasma and serum in a particular 24 hour interval. For example, in Figure 2, it can be seen that levels of urate in both the saliva and the plasma increase at night. This is because renal excretion is reduced during sleep and the urate must instead be eliminated in the gut via intestinal and salivary secretions. This effect can also be seen in Figure 3 (levels of urate in the urine decrease and plasma levels increase during sleep) and is explained on page 9, lines 17 to 28 of the specification. As a consequence of this daily variation in urate levels, it is beneficial to compare any salivary urate reading with a control value. This allows the daily variation to be taken into account and the likelihood of pre-eclampsia to be determined.

Nowhere in the obstetric prior art is this day/night variation of urate levels in the body described. Consequently, the claims, as amended herein, are not obvious over the cited references, since the obstetric references fail to take into account diurnal and day/night variations in urate body levels.

6. Conclusions

It is clear from the above that: 1) the association between plasma urate levels and pre-eclampsia is not well characterized; therefore, a person of skill the art of obstetrics would be sceptical about the suitability of measuring body urate levels to diagnose pre-eclampsia; 2) one skilled in the art of obstetrics would not use samples of saliva to test for levels of urate, since they consider levels of the urate in the body to be due to changes is renal excretion and hence not have an effect of the level of urate in the saliva; 3) the composition of one biological sample (for example plasma) cannot be used to determine or predict the composition of a different biological sample (for example saliva); 4) one skilled in the art would not take the teachings of studies on men with gout and use that to diagnose pre-eclampsia in pregnant women; and 5) obstetric studies of pre-eclampsia fail to take into account the importance of day/night variations in plasma and saliva urate levels, which is beneficial in understanding the invention and arriving at a diagnosis of pre-eclampsia. For these and the other reasons provided above, it is clear that the invention is not obvious over the cited references and challenges very real prejudices in the art of obstetrics.

Thus, the claimed invention is not obvious in view of the combination of cited references. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. §103(a) be withdrawn.

III. Conclusion

In view of the foregoing, Applicant respectfully submits that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Office is invited to contact Applicant's undersigned representative at 610.640.7859 if there are any questions regarding Applicant's claimed invention.

The Commissioner is hereby authorized to debit any underpayment of fee due or credit any overpayment to Deposit Account No. 50-0436

Respectfully submitted,

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